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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,387	MIDOH ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *2-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

[1] Claims 44-56 are pending.

Election/Restriction

[2] Applicants' election of the invention of Group I, claims 1 and 13-14, filed December 18, 2003, is acknowledged. It is noted that applicant did not indicate whether the election is made with or without traverse. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants' request for rejoinder of non-elected claims is acknowledged. Upon allowance of the claims of the invention, the non-elected claims will be evaluated for rejoinder according to *In re Ochiai*, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer,* 77 F.3d 422, 37 USPQ2d 1663 (Fed. Cir. 1996). As the claims of the elected invention are not yet allowable for the reasons set forth below, rejoinder is not yet required.

[3] Claims 2-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

[4] Claims 1 and 13-14 are being examined to the extent the claims read on the elected invention.

Information Disclosure Statement

[5] All references cited by applicants in the information disclosure statements (IDSs) filed July 22, 2003 and March 06, 2002 have been considered by the examiner. A copy of each IDS is attached to the instant Office action.

Specification/Informalities

[6] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Cyclic Depsipeptide Synthetase and Method for Recombinant Production".

Claim Objections

[7] Claim 13 is objected to as being dependent upon a non-elected claim. It is suggested that, for example, applicant amend the claim such that it no longer recites non-elected subject matter.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[8] Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn to a protein comprising SEQ ID NO:2 or variants thereof having cyclic depsipeptide synthetase activity. The

claim reads on a product of nature and should be amended to indicate the hand of the inventor, e.g., by insertion of "purified" or "isolated". See MPEP § 2105.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[9] Claims 1 and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

Claim 1 (in relevant part) is drawn to a protein comprising a genus of variants of SEQ ID NO:2 having cyclic depsipeptide synthetase activity and claims 13 and 14 are drawn to (in relevant part) a method for production thereof.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such

identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of claimed polypeptides, *i.e.*,, the polypeptide of SEQ ID NO:2 having N-methyl-cyclooctadepsipeptide synthetase activity. The specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of polypeptides encompasses species that are widely variant in both structure and function, including all proteins having any amino acid sequence that have any cyclic depsipeptide synthetase activity. As such, the disclosure of the single representative species of SEQ ID NO:2 is insufficient to be representative of the attributes and features of *all* species encompassed by the claimed genus of claimed/recited polypeptides. Given the lack of description of a representative number of polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[10] Claim(s) 1 and 13-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a SEQ ID NO:2, which has N-methyl-cyclooctadepsipeptide synthetase activity, and a method for the production thereof by culturing a host cell transformed with an expression vector encoding SEQ ID NO:2, does not reasonably provide enablement for *all* variants of SEQ ID NO:2 having *any* cyclic depsipeptide synthetase activity and methods for production thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass *any* polypeptide having *any* cyclic depsipeptide synthetase activity and methods for

production thereof. The broad scope of claimed/recited polypeptides is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. In this case the disclosure is limited to SEQ ID NO:2, which has N-methyl-cyclooctadepsipeptide synthetase activity, and a method for the production thereof by culturing a host cell transformed with an expression vector encoding SEQ ID NO:2.

- The lack of guidance and working examples: The specification provides only a single working example of the claimed polypeptide, i.e., SEQ ID NO:2, which has N-methyl-cyclooctadepsipeptide synthetase activity, and only a single working example of a polypeptide produced using a host cell transformed with a recombinant polynucleotide, i.e., SEQ ID NO:2. These working examples fail to provide the necessary guidance for making and the entire scope of claimed/recited polypeptides. The specification fails to provide guidance regarding those amino acids of SEQ ID NO:2 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining the desired activity.

- The high degree of unpredictability in the art: The amino acid sequence of a polypeptide determines the protein's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence

where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high degree of unpredictability in making the entire scope of polypeptides having the desired activity.

- The state of the prior art supports the high degree of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no certain method for reasonably predicting the effects of even a *single* amino acid mutation on a protein. Such mutations may even completely alter a protein's activity. As a representative example, Witkowski et al. (*Biochemistry* 38:11643-11650) teaches that a single amino

acid substitution results in conversion of the parent polypeptide's enzymatic activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

- The amount of experimentation required is undue: While methods of generating variants of a given polypeptide, *e.g.*, by site-directed mutagenesis, and methods of isolating variants of protein-encoding polynucleotides, *e.g.*,, hybridization, are known, it is not routine in the art to screen for *all* polypeptides having a substantial number of modifications, and having *any* cyclic depsipeptide synthetase activity, as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is

unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[11] Claim(s) 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Weckwerth et al. (*J Biol Chem* 275:17909; cited in the IDS filed March 06, 2002). Claim 1 is drawn to SEQ ID NO:2 or a variant of SEQ ID NO:2 having cyclic depsipeptide synthetase activity. Weckwerth et al. teach isolation of PFSYN, a polypeptide having depsipeptide synthetase enzymatic activity from the fungus *Mycelia sterilia* (see particularly page 17910, right column). Weckwerth et al. teach the isolated enzyme has the ability to synthesize all known natural cyclooctadepsipeptides of the PF1022 type (page 17909, abstract). This anticipates claim 1 as written.

[12] Claim(s) 1 and 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Leitner et al. (EP 0578616 A2). Claim 1 (in relevant part) is drawn to a variant of SEQ ID NO:2 having cyclic depsipeptide synthetase activity and claims 13-14 are drawn to a method of recombinantly producing said variant of SEQ ID NO:2 (claim 13) and

optionally (in relevant part) wherein the cyclic depsipeptide is a derivative of substance PF1022. Leitner et al. teach isolation of a polypeptide having cyclosporin synthetase enzymatic activity from the fungus *Tolypocladium niveum* (see particularly Example 1 at page 6). Leitner et al. teach a nucleic acid encoding cyclosporin synthetase (see Appendix A) and a method for production thereof (see particularly Examples 18-19 at pages 14-15). This anticipates claims 1 and 13-14 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[13] Claim(s) 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weckwerth et al. in view of Leitner et al., Matsudaira (*Methods Enzymol* 182:602-613), Wozney (*Methods Enzymol* 182:738-751), and Aoyagi et al. (US Patent 5,763,221). Claims 13 and 14 are drawn to a method of recombinantly producing and collecting SEQ ID NO:2 and variants thereof having depsipeptide synthetase activity (claim 13) and optionally wherein the cyclic depsipeptide is a derivative of substance PF1022 (claim 14).

Weckwerth et al. disclose the teachings as described above. Weckwerth et al. further teach PF1022A is an outstanding anthelmintic (page 17909, left column, bottom) and describe the use of purified PFSYN for cell free synthesis of PF1022A (page 17910,

right column, bottom). Weckwerth et al. do not teach a method for recombinant production of PFSYN.

At the time of the invention, the skill of an ordinarily skilled artisan was such that the artisan could use conventional techniques to: 1) obtain a partial amino acid sequence of a purified polypeptide; 2) synthesize a degenerate polynucleotide probe based on the partial amino acid sequence; 3) use the polynucleotide probe to screen a cDNA or genomic library and identify a full length cDNA or genomic clone; 4) construct expression vectors comprising the isolated cDNA or genomic clone; 5) transform a host cell with an expression vector comprising the isolated cDNA or genomic clone and 6) express the encoded polypeptide using the transformed host cell. As evidence of the state of the art at the time of the invention, Matsudaira teaches methods for the determination of N-terminal amino acid sequences (see pages 602-604), and Wozney teaches methods of using a purified protein to clone the corresponding encoding nucleic acid for expression of the encoded protein using a recombinant host cell (page 738). Wozney teaches the considerations for the selection of peptide candidates for the production of degenerate oligonucleotide probes, synthesis of oligonucleotide probes, screening of genomic or cDNA libraries, and isolation and amplification of cDNA or genomic clones (pages 738-751). The methods described by Matsudaira and Wozney were applied by Leitner et al., who provide an example of the cloning of a cyclic depsipeptide synthetase by partial sequencing of the amino acid sequence of cyclosporin synthetase (Example 9) to isolate clones comprising nucleic acids that hybridize to a cyclosporin synthetase-specific oligonucleotide (Example 10) in order to

isolate a nucleic acid encoding cyclosporin synthetase (Examples 11-12) for recombinant expression of cyclosporin synthetase in a host cell (Examples 17-19). Also, the state of art regarding transformation and recombinant expression of a protein using, as a host, the microorganism that produces PF1022 is represented by Aoyagi et al. (see Example 4).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Weckwerth et al., Leitner et al., Matsudaira, Wozney, and Aoyagi et al. to isolate a nucleic acid encoding PFSYN and to recombinantly express and isolate the encoded protein. One would have been motivated to recombinantly express PFSYN in order to generate a relatively larger amount of protein than can be obtained non-recombinantly and to purify PFSYN in order to synthesize PF1022A *in vitro* as taught by Weckwerth et al. One would have a reasonable expectation of success for isolating the nucleic acid encoding PFSYN and to recombinantly express and isolate the encoded protein because of the results of Weckwerth et al., Leitner et al., Matsudaira, Wozney, and Aoyagi et al. Therefore, claims 13 and 14, drawn to a method for producing a cyclic depsipeptide synthetase as described above would have been obvious to one of ordinary skill in the art.

[14] Applicant's claim for foreign priority under 35 USC § 119(a)-(d) in the declaration filed February 07, 2002, is acknowledged. If applicant traverses a rejection based on the date of a foreign priority reference, applicant should perfect a claim to foreign priority by providing English-language translations of the foreign priority documents (see MPEP § 706.02(b)).

Conclusion

[15] Status of the claims:

- Claims 1-14 are pending.
- Claims 2-12 are withdrawn from consideration.
- Claims 1 and 13-14 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

01-15-04

DAVID STEADMAN
PATENT EXAMINER